CLAIM AMENDMENTS

1. to 42. **(Canceled)**

43. **(Currently amended)** A method for treating ~~an arthritic or inflammatory condition~~ arthritis or reducing inflammation in a subject, comprising administering to the subject a protein that causes TNF receptor to be released from human cells in which TNF receptor is expressed.

44. **(Previously Presented)** The method of claim 43, wherein the protein is a metalloprotease.

45. **(Currently amended)** The method of claim 43, wherein the protein ~~cleaves~~ causes cleavage of the human p55 TNF receptor.

46. **(Currently amended)** The method of claim 43, wherein the protein has at least one of the following properties:

a) it comprises the amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:8;

b) it comprises the amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:9; or

c) it comprises a consecutive amino acid sequence that is at least 80% identical to a) or b) (or fragment thereof) which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

47. **(Currently amended)** A method for treating an arthritic or inflammatory condition in a subject, comprising administering to the subject a protein having at least one of the following properties:

a) it comprises ~~a~~ an amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:8; or

b) it comprises a consecutive amino acid sequence that is at least 80% identical to a) (or fragment thereof) which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

48. **(Currently amended)** The method of claim 47, ~~wherein the condition is~~ whereby the subject is treated for sepsis.

49. **(Currently amended)** The method of claim 47, ~~wherein the condition is~~ whereby the subject is treated for arthritis.

50. **(Currently amended)** The method of claim 49, ~~wherein the condition is~~ whereby the subject is treated for rheumatoid arthritis.

51. **(Currently amended)** The method of claim 47, wherein the protein comprises ~~a~~ an amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:8.

52. **(Currently amended)** The method of claim 47, wherein the protein comprises a fragment of the amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:8, which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

53. **(Currently amended)** The method of claim 47, wherein the protein comprises a consecutive sequence that is at least 80% identical to the amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:8 (or fragment thereof), which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

54. **(Currently amended)** The method of claim 47, wherein the protein comprises a consecutive sequence that is at least 95% identical to the amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:8 (or fragment thereof), which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

55. **(Previously Presented)** The method of claim 47, wherein the protein is a metalloprotease.

56. **(Currently amended)** The method of claim 47, wherein the protein ~~cleaves~~ causes cleavage of the human p55 TNF receptor.

57. **(Currently amended)** A method for treating ~~an arthritic or inflammatory condition~~ arthritis or reducing inflammation in a subject, comprising administering to the subject a protein having at least one of the following properties:

a) it comprises ~~a~~ an amino acid sequence encoded in the longest open reading frame of ~~SEQ. ID NO:8~~ SEQ. ID NO:9; or

b) it comprises a consecutive amino acid sequence that is at least 80% identical to a) (or fragment thereof) which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

58. **(Currently amended)** The method of claim 57, ~~wherein the condition is~~ whereby the subject is treated for sepsis.

59. **(Currently amended)** The method of claim 57, ~~wherein the condition is~~ whereby the subject is treated for arthritis.

60. **(Currently amended)** The method of claim 59, ~~wherein the condition is~~ whereby the subject is treated for rheumatoid arthritis.

61. **(Currently amended)** The method of claim 57, wherein the protein comprises ~~a~~ an amino acid sequence encoded in the longest open reading frame of ~~SEQ. ID NO:8~~ SEQ. ID NO:9.

62. **(Currently amended)** The method of claim 57, wherein the protein comprises a fragment of the amino acid sequence encoded in the longest open reading frame of ~~SEQ. ID NO:8~~ SEQ. ID NO:9, which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

63. **(Currently amended)** The method of claim 57, wherein the protein comprises a consecutive sequence that is at least 80% identical to the amino acid sequence encoded in the longest open reading frame of ~~SEQ. ID NO:8~~ SEQ. ID NO:9 (or fragment thereof), which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

64. **(Currently amended)** The method of claim 57, wherein the protein comprises a consecutive sequence that is at least 95% identical to the amino acid sequence encoded in the longest open reading frame of ~~SEQ. ID NO:8~~ SEQ. ID NO:9 (or fragment thereof), which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

65. **(Previously Presented)** The method of claim 57, wherein the protein is a metalloprotease.

66. **(Currently amended)** The method of claim 57, wherein the protein ~~cleaves~~ causes cleavage of the human p55 TNF receptor.

67. **(Withdrawn - Currently Amended)** A pharmaceutical composition comprising a protein formulated in an excipient for administration to a human patient, wherein the protein has at least one of the following properties:

a) it comprises the amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:8;

b) it comprises the amino acid sequence encoded in the longest open reading frame of SEQ. ID NO:9;

c) it comprises a consecutive amino acid sequence that is at least 80% identical to a) or b) (or fragment thereof) which ~~cleaves~~ causes cleavage of TNF receptor from human cells in which TNF receptor is expressed.

68. **(Withdrawn - Currently Amended)** The pharmaceutical composition of claim 64, packaged in a kit with instructions for treating ~~an arthritic condition~~ arthritis.

69. **(Withdrawn - Currently Amended)** The pharmaceutical composition of claim 64, packaged in a kit with instructions for ~~treating an inflammatory condition~~ reducing inflammation.

70. **(New)** The method of claim 47,-whereby the subject is treated for multiple sclerosis.

71. **(New)** The method of claim 47,-whereby the subject is treated for sepsis.

72. **(New)** The method of claim 57, whereby the subject is treated for multiple sclerosis.

73. **(New)** The method of claim 57, whereby the subject is treated for sepsis.

74. **(New)** The pharmaceutical composition of claim 64, packaged in a kit with instructions for treating multiple sclerosis.

75. **(New)** The pharmaceutical composition of claim 64, packaged in a kit with instructions for treating sepsis.

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 43-69 were previously pending in the application. Claims 67-69 are withdrawn from consideration. Certain claims are amended as indicated above, and claims 70-75 are added. Claims 70-73 fall within the group under examination; and Claims 74-75 fall within the group withdrawn from examination. Accordingly, Claims 43-66 and 70-73 are currently under consideration.

Some claims have been amended to refer to SEQ. ID NO:9 rather than SEQ. ID NO. 8, at applicants' option, as being an embodiment of current commercial interest. Both SEQ. ID NO:8 and SEQ. ID NO:9 are in the group under examination (claim 46). The other amendments do not narrow the claimed invention. Accordingly, the claims cover all equivalents to which applicants were previously entitled.

Claims 43-66 as previously presented are clear of the prior art of record, but stand rejected under 35 USC § 112.

Interview Summary

Applicants wish to thank Examiners Joseph F. Murphy and Yvonne Eyler for the interview conducted with the undersigned and with Michael Schiff on March 26, 2003, during which the rejections under §112 ¶ 1 were discussed.

The amendments and remarks provided here are in conformity with the arguments presented, as well as with the suggestions of the Examiners, for which applicants are grateful. The application is now believed to be in condition for allowance, which is respectfully requested.

Rejections Under 35 USC § 112 ¶ 1

Claims 43-66 were rejected as not meeting the enablement and description requirements of 35 USC § 112 ¶ 1. The Office Action indicates that the specification is enabling for treatment of septic shock by administering [a protein containing an amino acid sequence encoded in] SEQ. ID NOs:8 or 9. However, concerns are raised about the use of fragments and variants of said proteins, and other proteins falling within the scope of claim 43; and for the treatment of other inflammatory conditions.

Applicants respectfully disagree. Each of these points will be considered in turn.

Fragments and variants of SEQ. ID NOs:8 and 9:

The Office Action indicates that there are a large number of species that are fragments of [proteins encoded in] SEQ. ID NOs:8 and 9, or at least 80% identical. It infers that experimentation would be required to identify which species within the claimed genus would be effective.

The written description requirement is satisfied, because the claims require not only a degree of homology with the prototype sequences, but also an expressly stated function. Specifically, the protein must have the property of causing cleavage of TNF receptor from human cells in which TNF receptor is expressed. Any protein that does not have both the stated structural requirements and the stated functional requirements is excluded from coverage. This is in compliance with the Written Description Guidelines Training Materials, promulgated by the Office. See especially Example 9.

The enablement requirement is satisfied, because a reasonable proportion of species within the genus will have the recited function, and the functional species can be identified without undue experimentation.

In re Wands (8 USPQ2d 1400, Fed. Cir. 1988) sets the standard by which "undue experimentation" would prevent patenting of an invention under the enablement requirement of § 112 ¶ 1. The Wands patent claims an assay method using an antibody described only as being of the IgM class, and having certain functional properties.[1] Based only upon amino acid sequence, the number of antibody molecules that would fall within the Wands claim is enormous.[2] Still, the Federal Circuit found that the skilled artisan could obtain other IgM antibodies falling within the claim without undue experimentation — in spite of the considerable number of variant structures from which to chose. Even

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[1] Claim 1 of U.S. Patent 4,879,219 (J.R. Wands et al.) reads as follows: An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of: contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and determining the presence of said substance in said sample; wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}.

[2] At least 6.25×10^{82}, using conservative assumptions. This number is derived as follows. Variation between antibody molecules is assumed to occur only in the hypervariable region, about 50 different amino acid positions in both the heavy and light chains which could have any one of the 20 different naturally occurring amino acid residues. Assume also that there are about 25 variable region genes available for the heavy chain, and about 25 variable region genes available for the κ or λ light chain. Irrespective of function, the number of possible antibody molecules is therefore at least $(50^{20} \times 25)^2 = 6.25 \times 10^{82}$.

if only about 2.8% of the hybridomas made according to the description fell within the claim, the Court held that Wands was fully enabled, because it was standard practice to screen negative hybridomas in order to find one that makes the desired antibody.[3]

Fragments of proteins encoded in SEQ. ID NOs:8 and 9 that cause TNF receptor release can readily be identified by employing standard methodology for functionally mapping. The skilled reader would know to make recombinant protein which is trimmed at the N- or C-terminus, and then test it for function as described in Example 1, or by any other suitable method. Trimming would continue until activity is lost, at which point the minimum functional unit of the protein would be identified. Fragments containing any portion of the protein down to this size would be functional, as would be fusion constructs containing at least the functional core of the protein.

To generate variants that incorporate one or more amino acid changes, the skilled reader can change particular residues and retest for activity. There is no need to target the mutations to particular positions in the sequence. An effective way to generate a large collection of functional variants is to use a random mutation strategy. The standard texts *Protocols in Molecular Biology* (Ausubel et al. eds.) and *Molecular Cloning: A Laboratory Manual* (Sambrook et al. eds.) describe techniques employing chemical mutagenesis, cassette mutagenesis, degenerate oligonucleotides, mutually priming oligonucleotides, linker-scanning mutagenesis, alanine-scanning mutagenesis, and error-prone PCR. Other efficient methods include the E. coli mutator strains of Stratagene (Greener et al., Methods Mol. Biol. 57:375, 1996) and the DNA shuffling technique of Maxygen (Patten et al., Curr. Opin. Biotechnol. 8:724, 1997; Harayama, Trends Biotechnol. 16:76, 1998). To the extent that the user may wish to test variants near the outer limit of variability in the claims (i.e., only ~90% identical to SEQ ID NO:2), they may subject the representative sequence to successive cycles of mutation and functional testing — or choose a mutation strategy that generate more abrupt changes, such as the DNA shuffling technique.

There are several commercially available services and kits available to the skilled reader to use in obtaining variants of the claimed proteins. By way of illustration, enclosed with this Amendment is information regarding the GeneTailor™ Site-Directed Mutagenesis System sold by InVitrogen™ Life Technologies (Exhibit 1). By employing this type of system in conjunction with the functional screening assay of Example 1, variants can be generated and tested in a high throughput manner.

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[3] *In re Wands, op. cit.*, 8 USPQ2d at 1406-07.

Other proteins having the claimed function

Claim 43 covers a method for treating arthritis or reducing inflammation in a subject, comprising administering to the subject a protein that causes TNF receptor to be released from human cells in which TNF receptor is expressed. Claim 44 further requires the protein to be a metalloprotease. Claim 45 further requires that the protein be able to cause cleavage of the p55 isoform of the TNF receptor.

These claims are in compliance with the requirements of 35 USC § 112 by defining the protein according to its function. This is explicitly permitted under § 112 ¶ 6. Claim 43 has the same meaning as a claim presented in the following form:

> 43. A method for treating an arthritic or inflammatory condition arthritis or reducing inflammation in a subject, comprising administering to the subject a protein means for causing TNF receptor to be released from human cells in which TNF receptor is expressed.

The protein [means] that causes TNF receptor to be released from the surface of cells is illustrated in the specification not only as the proteins encoded in SEQ. ID NOs:8 and 9, their fragments and variants, but also by proteins encoded in SEQ. ID NOs:1 to 7 and SEQ. ID NO:9. Protein expressed from SEQ. ID NOs:4 and 6 are shown to prevent septic shock in Example 6. A further illustration is provided in the form of TRRE purified from PHA stimulated THP-1 cells in Example 2, and tested in the septic shock model in Example 3.

In addition, the specification provides a system by which the reader may obtain and test other proteins to determine if they cause release of TNF receptors according to the invention. Example 1 describes an assay system in which a protein is tested for its ability to release TNF receptor from a cell line transfected to express TNF receptors in a high density and stable fashion. Receptor release is measured either by quantitating the receptor released into the medium by immunoassay, or the receptor left on the cell surface by immunofluorescence. Example 1 further describes how to determine whether the protein is a metalloprotease, by conducting assays in the presence of metal chelators and other inhibitors. To obtain additional proteins for testing according to the assay system, the reader may use

any source of their own devising — or they may implement the functional screening process using a cDNA library from an inflammatory regulatory cell according to the system illustrated in Example 5.

Thus, the skilled reader is equipped to practice the invention embodied in Claim 43 by using any one of over 10 different protein preparations exemplified in the specification, or by obtaining and testing other protein preparations having the desired activity as directed. Claims 43-46 are in compliance with the form permitted in 35 USC § 112 ¶ 6, and meet the description and enablement requirements of § 112 ¶ 2.

This disclosure and the priority applications are the first to show that it is possible to treat inflammatory disease using protein that causes TNF receptor shedding. There is no prior art of record to suggest that inflammatory conditions with a protein having this function. Accordingly, applicants are entitled to protection of the invention defined according to its function, pursuant to 35 USC § 112 ¶ 6.

Treatment of other inflammatory conditions

The disclosure provides a full description of the importance of the TNF pathway in mediating inflammatory reactions, and the potential for treating inflammatory conditions by preventing TNF receptor transduction using the receptor releasing proteins of this invention. Examples 2 and 6 illustrate the treatment methods of the invention in an animal model for septic shock. The specification is enabling for the treatment of other inflammatory conditions, because the formulation and administration of the therapeutic agent for other conditions can follow the same procedure as in the septic shock model, or adapted to the condition in accordance with standard protocols known in the art of preparing biological agents for therapeutic administration.

Enclosed with this Amendment is a written presentation prepared by Meyer Pharmaceuticals (Exhibit 2), the licensee of this invention. A number of other animal models are used to demonstrate the broad therapeutic spectrum of the proteins of this invention.

- Pages 23-26 provide further illustration of the treatment of septic shock, showing that the protein is stable and has a long lasting effect.
- Pages 28-33 illustrate the treatment of arthritis, using the Collagen-Induced Arthritis (CIA) model (Courtenay et al., Nature 283:666, 1980). This is a broadly accepted animal model for the testing of agents for human therapy.

- Page 35 illustrates treatment using a standard model for carrageenan-induced edema (Winter CA et al., Proc Soc Exp Biol Med 111:544, 1962).
- Page 36-37 illustrates treatment of Experimental Autoimmune Encephalomyelitis (EAE), an established model for Multiple Sclerosis (Brown et al., Lab. Invest. 45:278, 1981).
- Page 38 illustrates the treatment of experimentally induced asthma.

These results confirm that the treatment of inflammatory conditions using the TNF receptor releasing proteins of this invention is described and enabled in the specification.

The Office Action cites an unspecified reference by Gabay as indicating that agents successful for improving the clinical and biological signs of inflammation in arthritis may not work in a percentage of the patient population. Of course, very few therapeutic agents work on 100% of the patents treated, even those that are patented and approved for commercial distribution. The specification illustrates (and more recent data confirms) that the TNF receptor releasing proteins of this invention are efficacious to a significant degree in a significant proportion of the population. This satisfies the utility requirements of 35 USC §§ 101 and 112 ¶ 1. Further scrutiny of the therapeutic methods of this invention is the responsibility of the Food & Drug Administration, not the U.S. Patent & Trademark Office.

Applicants respectfully submit that the claims currently under examination meet the enablement and written description requirements of 35 USC § 112 ¶ 1. Withdrawal of these rejections is requested.

Rejection Under 35 USC § 112 ¶ 2

Claims 43-66 were rejected as being indefinite. Specifically, Claim 43 was rejected for recitation of the term "arthritic or inflammatory condition."

Applicants respectfully disagree that the term is indefinite, since the skilled reader will know how to identify an arthritic condition or an inflammatory condition based on standard medical criteria. Nevertheless, the claim wording has been amended to remove the term objected to, and replace it with the term suggested in the interview. Withdrawal of this rejection is respectfully requested.

Conclusion

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided below.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-007CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Sept 8, 2003

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Enclosures:

Exhibit 1: GeneTailor™ Site-Directed Mutagenesis System sold by InVitrogen™ Life Technologies

Exhibit 2: Meyer Pharmaceuticals, Inc., Corporate presentation entitled "Tumor Necrosis Factor Receptor Releasing Enzyme: A new family of therapeutic agents for treating arthritis and other inflammatory conditions"

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